TheScientist

The Scientist 9[16]:, Aug. 21, 1995

News

Drug Institute Tackles Neurology of Addiction

By Karen Young Kreeger

Author: Karen Young Kreeger

Tracing its origin back 60 years to the Research Division of the United States Narcotics Farm--a treatment facility for opiate addicts located in Lexington, Ky.--the National Institutes of Health's National Institute on Drug Abuse (NIDA) has grown into the world's largest drug addiction research facility.

Sidebar: DISCUSSING THE SCIENCE BEHIND DRUG ADDICTION

"This institute intramurally and extramurally provides 85 percent of the world support for research on drug abuse and addiction," remarks Alan I. Leshner, NIDA's director. "Our 1995 total budget for all of that is $437 million." While stressing that the figure is not large, he acknowledges that "that's not a bad budget by general NIH standards": Seven out of the 17 institutes have larger budgets. According to the 1995 budget report of the Office of National Drug Control Policy (ONDCP), $1.2 billion was spent by the united States government on preventing drug abuse.

addiction from the molecules up.

The thrust of the institute's massive effort revolves around a single tenet: NIDA research is based on the definition of drug addiction as a chronic relapsing disease of the brain, which is expressed in behavioral ways and occurs in a social context--as opposed to being (as it is often considered) primarily a social problem. Leshner, who served as acting director of the National

Institute of Mental Health (NIMH) from 1990 to 1992, sees NIDA's mission as shaped by two interconnected approaches to the science and policy of understanding and combating drug addiction.

"First, NIDA's year 2000 goal is to have science replace ideology as the foundation of the nation's drug abuse prevention, treatment, and policy strategies." Second, because of this all-encompassing way of thinking about addiction, he asserts that NIDA has "an extraordinarily wide breadth of disciplines to support, from the most molecular- and cellular-oriented disciplines to anthropology and sociology."

The bulk of this wide-ranging research is conducted through extramural research grants--about 94 percent of NIDA's total 1995 budget, or $412 million. The other 6 percent, or $25 million, goes to support the nearly 100 intramural scientists currently working at the Baltimore-based Addiction Research Center (ARC). The Kentucky rehabilitation facility was renamed ARC in 1948 and in 1979 was relocated to Baltimore.

MAJOR PLAYER: "The institute provides 85 percent of the world support for research on drug abuse," states NIDA director Alan Leshner. One primary area of study is mapping the neurological effects of drugs, says intramural scientist Edythe London, shown here with a PET image of a human brain.

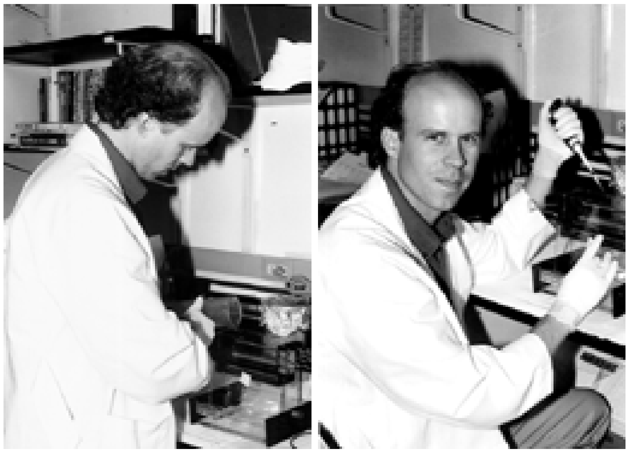
Last March, reflecting NIDA's increasingly broad scope of disciplines, Leshner reorganized the extramural research program to enhance AIDS research--because of the growing risk of HIV infection among drug users--and to infuse neuroscience throughout the program's four research divisions (basic; clinical and services; epidemiology and prevention; and medications development). NIDA's Office on AIDS increased its full-time staff from one to four people. Meanwhile, a newly created etiology and clinical neurobiology branch represents some of the expansion of NIDA neuroscience research, officials say.

The reorganization, says Leshner, also helped the institute comply with the Clinton administration's efforts to streamline government agencies. The six branches of intramural research at NIDA--clinical pharmacology, preclinical pharmacology, neuroscience, etiology, treatment, and molecular neurobiology--however, remain unchanged.

To get at the root neurological causes and mechanisms of addiction, NIDA-supported researchers have been identifying and mapping the brain regions and proteins that play a role in reinforcing--biochemically and behaviorally--the addictiveness of drugs. "The broad way to look at addiction research is that humans are driven by reward systems at molecular, neuronal, and behavioral levels," explains George Uhl, chief of the molecular neurobiology research branch and acting scientific director of intramural research.

However, to first understand how these complex systems work, scientists from NIDA, NIMH, and here identified binding sites on brain cells for every major substance of abuse--opiates, cocaine, nicotine, phencyclidine (PCP, or "angel dust"), and tetrahydrocannabinol (THC), the active ingredient in marijuana.

"Then, over the last six or seven years, a major thrust of my own lab has been to define the molecular nature of these sites by finding their genes and cloning them," relates Uhl. "We now know the primary molecular target for each of the major classes of these drugs." The biochemistry of how cocaine affects neurons was determined by Uhl's team, for example. It works by blocking the dopamine transporter, thus eliminating the uptake of dopamine by neurons. Dopamine concentrations then increase in synapses, causing a cascade of molecular events that is thought to create the euphoric effects associated with cocaine.[ref tk]



"What we don't understand much about are the events that go on subsequent to the drug binding to a particular receptor on the nerve cell," adds one of Uhl's colleagues, David Vandenbergh, a senior staff fellow in the intramural molecular neurobiology section. "What are the things going on inside the cell after the binding?"

studies individual variability in response to a particular drug. "What we hope to do is to begin to understand which neuronal and biochemical pathways are important in drug addiction by looking at genetic differences in response to drugs," he remarks. "What we'd like to find is something like a form of the dopamine transporter that takes up dopamine slower or faster or a form that binds cocaine better or worse. But we haven't found that kind of a difference yet."

While Vandenbergh looks for differences in genetic predisposition to addiction, medicinal chemist Amy Hauck Newman, a senior staff fellow in the intramural preclinical pharmacology branch, designs novel compounds for use in drug rehabilitation programs, as well as basic studies in brain binding sites. The main biochemical target her team works with is also the dopamine transporter. Instead of looking at the receptor itself, Newman and colleagues study chemicals that interact with the receptors, mainly a compound with structural features similar to cocaine known as a benztropine analogue.

"Benztropine is interesting to us because it binds to the dopamine transporter like cocaine, but unlike cocaine, animals behave differently when given the analogue," she notes. "Benztropines are not locomotor stimulants, for example. Because of this difference, we might be able to develop therapeutic drugs that are chemically like cocaine, but not behaviorally like cocaine."

To view changes in brain chemistry from a larger perspective, NIDA is building its own positron emission tomography (PET) facility, which is funded in part by ONDCP. Since the early 1980s, Edythe D. London, chief of NIDA's neuroimaging and drug action section, has focused on using PET to map the effect of such psychoactive drugs as opiates.

"We need to remember that the brain is highly interconnected. If you merely map the receptors for drug action, you have an incomplete picture because a drug's effect can propagate to sites that are quite remote from the initial receptor targets," explains London.

"We've mapped the distribution of the response to most classes of abused drugs and have also delineated the distribution of the withdrawal syndrome to opiates. We found that when these drugs were given at doses that produced a positive affective state, the response was a reduction in cerebral glucose metabolism in human volunteers. Clearly what we're seeing with the glucose metabolism maps is an effect downstream from the drug binding to the receptor."

An upcoming article in Neuropsychopharmacology (E.D. London et al., 13:21-31, in press) from London's group shows that substance abusers have a lower glucose metabolic rate in posterior areas of the cortex, including the visual association cortex. In addition, the drug abusers have elevated activity in the orbitofrontal region. According to London, this area is implicated in at least one other psychiatric condition involving a lapse in impulse control--obsessive-compulsive disorder. "It's not a very large jump for us to think about drug abuse as a disorder that involves a lapse of impulse control," she observes.

Other NIDA-supported scientists also study addiction on a brain-region scale. Extramural grantee Eric J. Nestler, Elizabeth Mears and House Jameson Professor of Psychiatry and Pharmacology at Yale University, and colleagues study molecular events that occur in parts of the mesolimbic dopamine system (for a review, see D.W. Self and E.J. Nestler, Annual Reviews in Neuroscience, 18:463-95, 1995). "This system arises from dopamine-producing neurons located in the ventral tegmental area of the midbrain and includes projections of these neurons to frontal brain regions, such as the nucleus accumbens," he explains.

"It's generally thought that this system plays an important role in some very basic functions, including things like motivation and volition--whatever it takes to get a person moving in a goal-oriented, directed way.

"We've been able to provide some evidence that changes in the levels of certain [brain] proteins actually are responsible for some of the behavioral changes seen in drug addiction. For example, we're able to show that a signal transduction protein called protein kinase-A is altered in the nucleus accumbens by chronic exposure to cocaine, opiates, and alcohol. When we take an animal that's self-administering cocaine or heroin, we can go into these brain areas and activate this kinase and see the animal self-administer the drug." Nestler calls this "a critical finding" because it relates the biochemical aspects to the behavioral phenomenon of addiction.

"Another area of research shows that some of the changes that we see in the neurons of the ventral tegmental area look somewhat like what we see with injured neurons," he remarks. "Drugs such as morphine do produce very prominent structural changes in these neurons--they retract and shrink."

Prompted by the cocaine and crack epidemics of the 1980s and 1990s, working out the science behind addiction of such acutely addictive substances as cocaine and heroin has been a primary concentration of NIDA-supported research for the last 10 years. Recently, more effort has been placed on examining the physiological effects of two other well-known abused substances--nicotine and THC.

branch chief Jack Henningfield investigates the nicotine-withdrawal syndrome, which includes applying electrophysiological measures such as electroencephalograms (EEGs). "In one study, heavy smokers stayed in our residential ward for about one month," relates Wallace Pickworth, senior pharmacologist in the clinical pharmacology branch. "We deprived them of cigarettes for 10 days. Their EEG readings slowed down during nicotine withdrawal. On the first day that they could smoke, all of them did--with great rapacity. Even within as early as one to two cigarettes after, their EEG returned to its pre-withdrawal level."

These and other findings led Pickworth and other NIDA scientists to establish the idea that there were physiological withdrawal symptoms--changes in brain waves and heart rate, for example--associated with stopping smoking, not simply a mental craving to light up [ref tk]. Pickworth says physiological information like this is helpful in developing nicotine replacement therapies.

The National Conference on Marijuana Use, Prevention, Treatment, and Research, a meeting sponsored by NIDA and held last month in Washington, D.C., marked the first time that basic scientists got together with drug prevention and treatment specialists in this area of study, says Billy Martin, the Harris Professor of Pharmacology at the Medical College of Virginia. Martin, a NIDA extramural grantee, gave a talk on the first rodent-based dependence model for THC. In this experiment, THC-habituated rodents that were given a THC-receptor blocker produced opiate-like withdrawal symptoms (M.D. Aceto et al., European Journal of Pharmacology, in press).

Although the main thrust of NIDA's basic molecular biological studies is to understand the biochemistry and neuroscience of addiction, its research also has implications for answering one of neuroscience's ultimate questions: how memory and learning work. London has been using PET imaging in this area. "In one study, we exposed individuals who habitually use cocaine to stimuli related to drug-taking, such as a video of pictures of drug paraphernalia," she relates.

"We also put them in a control situation where they see a video of more neutral cues. When we compare the PET data from the two situations, we see an activation of the entire cerebral cortex [when individuals view the more stimulating video], including the parahippocampal gyrus, a part of the brain that is probably involved in recalling the memories of the cocaine-taking experience. So basically what we see are cortical circuits that are activated by visual cues, which elicit memories with an emotional context."

"I think that [cellular basis of drug addiction] is a great system in which to study the underpinnings of memory and learning because drugs provide exquisite control over input to the brain--they are pharmacologically defined," says Uhl. "This work can address a big question in neurobiology: How do molecular and circuit changes, maybe even changes at the gene expression level, help define memory-like processes?"

(The Scientist, Vol:9, #16, pg.12 , August 21, 1995)
(Copyright © The Scientist, Inc.)

***The Scientist* 9[16]:, Aug. 21, 1995**